AMENDMENTS TO THE SPECIFICATION

IN THE SPECIFICATION:

PAGE 2

Please replace the paragraph beginning at line 2, through line 11, with the following new paragraph:

② Tetrahedron Letters (Tetrahedron Lett.), 28, 4935 (1987); a method for producing an optically active ~~3-(R)-alkoxyglutaric~~ (R)-3-acyloxyglutaric acid monomethyl ester and a ~~3-(R)-alkoxyglutaric~~ (R)-3-acyloxyglutaric acid monomethyl ester by acting α-chymotrypsin on a 3-alkoxyglutaric acid dimethyl ester and a 3-acyloxyglutaric acid dimethyl ester in a buffer to carry out hydrolysis is disclosed. However, in this method, there are problems that an amount of oxygen to be used is too much, and an optical purity of the objective compound is low.

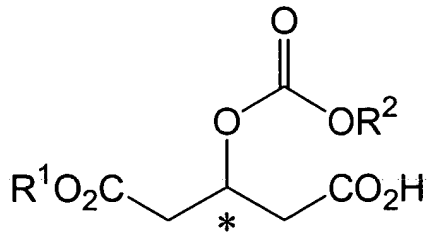
Please replace the paragraph beginning at line 12, through line 21, with the following new paragraph:

③ Journal of Organic Chemistry (J. Org. Chem.), 61,6024 (1996); a method for producing an optically active ~~3-(S)-acetyloxyglutaric~~ (S)-3- acetyloxyglutaric acid monoester by hydrolyzing a ~~3-acetyloxymonoglu~~ 3-acetyloxymonoglu acid diester in a mixed solvent of a phosphate buffer with a pH of 7 and 1,4-dioxane in the presence of a lipase originated from *Candida Antarctica* is disclosed. However, in this method, there are problems that an amount of oxygen to be used is too much, an optical purity of the objective compound is low and high carcinogenic 1,4-dioxane must be used with a large amount.

PAGE 3

Please replace the paragraph beginning at line 25, through page 4, line 3, with the following new paragraph:

An object of the present invention can be also accomplished by an optically active 3-substituted oxyglutaric acid monoester compound represented by the formula (IV):



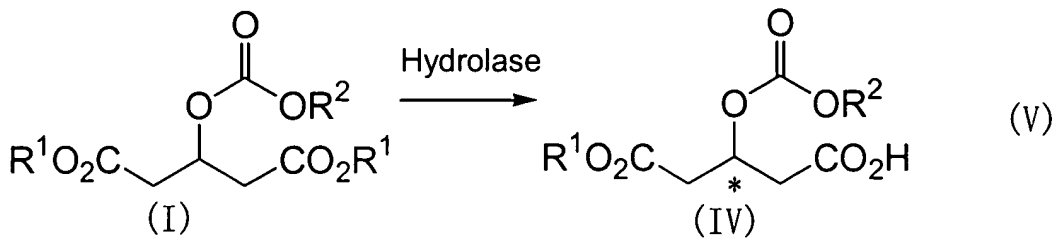
(IV)

wherein R^1 and R^2 have the same meanings as defined above and * means an symmetric carbon.

PAGE 13

Please replace the paragraph beginning at line 7, through line 20, with the following new paragraph:

In the hydrolysis reaction for obtaining the optically active 3-substituted oxyglutaric acid monoester compound of the present invention, for example, one of the ester groups of the 3-substituted oxyglutaric acid diester (in the following, sometimes referred to as Compound (I).) represented by the above-mentioned formula (I) is selectively hydrolyzed in the presence of a hydrolase to obtain an optically active 3-substituted oxyglutaric acid monoester (in the following, it may be sometimes called to as Compound (IV).) represented by the formula (IV) as mentioned in the following formula (V):



wherein R^1 and R^2 have the same meanings as defined above and * means an asymmetric carbon.

PAGES 15-18

Please replace the paragraphs beginning at line 30, through page 18, line 30, with the following new paragraphs:

Specific examples of Compound (IV) obtained by the hydrolysis reaction of the present invention may include, for example,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monoethyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monopropyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monobutyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monopentyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monohexyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monoheptyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monooctyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mononononyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monodecyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monoisopropyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-s-butyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-t-butyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monochloromethyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monobenzyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-4-nitrobenzyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-4-trifluoromethylbenzyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-4-chlorobenzyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-4-bromobenzyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-4-fluorobenzyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active mono-4-methoxybenzyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monovinyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monoallyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(2-methylbenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(3-methylbenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(4-methylbenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(2-methoxybenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(3-methoxybenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(4-methoxybenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(2-chlorobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(3-chlorobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(4-chlorobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(2-bromobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(3-bromobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(4-bromobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(2-fluorobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(3-fluorobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(4-fluorobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(2-nitrobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(3-nitrobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(4-nitrobenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(2-methoxybenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(3-methoxybenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(4-methoxybenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-(t-butoxybenzyl)oxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-methoxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-isopropoxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-phenoxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-vinyloxycarbonyloxyglutarate,

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-allyloxycarbonyloxyglutarate,

and the like, preferably

optically active monomethyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyoxyglutarate, and/or

optically active monoethyl ~~3-(R or S)-~~(R or S)-3-benzyloxycarbonyoxyglutarate,

is/are used.

PAGE 19

Please replace the paragraph beginning at line 19, through line 31, with the following new paragraph:

Incidentally, physical properties of the 3-benzyloxycarbonyloxyglutarate dimethyl ester were as follows.

^{1}H-NMR (δ (ppm), $CDCl_3$): 2.71-2.81 (m, 4H), 3.66 (s, 6H), 5.16 (s, 2H), 5.43 (quintet, 1H), 5.75 (m, 1H), 7.33-7.37 (m, 5H)

^{13}C-NMR (δ (ppm), $CDCl_3$): 38.2, 51.9, 69.8, 70.7, 128.3, 128.57, 128.60, 135.1, 154.1, 170.0

MS (EI) m/z: 310 (M^+)

MS (CI, i-C_4H_{10}) m/z: 311 (MH^+)

Elemental analysis; Calcd: C, 58.05%; H, 5.86%

Found: C, 57.43%; H, 5.88%

Example 2 (Synthesis of optically active ~~3-(S)-~~(S)-3-benzyloxycarbonyloxyglutaric acid monomethyl ester)

Please replace the paragraphs beginning at line 32, through page 20, line 27, with the following new paragraphs:

To 721 mg (2.32 mmol) of dimethyl 3-benzoyloxycarbonyloxyglutarate were added 2 ml of an aqueous enzyme solution in which 72 μg of a lipase (CAL; available from Roche AG, Chirazyme L-2 (trade name)) originated from *Candida antarctica* and 195 mg (2.26 mmol) of

sodium hydrogen carbonate had been dissolved, and the mixture was reacted at 30°C for 7 hours under stirring. After completion of the reaction, 10 ml of ethyl acetate was added to the obtained reaction mixture, a pH of the aqueous layer was adjusted to 1.9 by using 2 mol/L hydrochloric acid, 700 mg of sodium chloride was added to the mixture and the mixture was extracted. The obtained organic layer was dried over anhydrous magnesium sulfate, filtered and then concentrated under reduced pressure to obtain 675 mg (isolation yield based on dimethyl 3-benzyloxycarbonyloxyglutarate=98%) of an optically active monomethyl ~~3-(S)-~~(S)-3-benzyloxycarbonyloxyglutarate.

Incidentally, optically active monomethyl ~~3-(S)-~~(S)-3-benzyloxycarbonyloxyglutarate is a novel compound shown by the following physical properties.

^{1}H-NMR (δ (ppm), $CDCl_3$): 2.74-2.83 (m, 4H), 3.66 (s, 3H), 5.16 (s, 2H), 5.41 (quintet, 1H, J=6.35Hz), 7.32-7.37 (m, 5H), 9.55 (brs, 1H)

^{13}C-NMR (δ (ppm), $CDCl_3$): 37.94, 37.99, 52.0, 69.9, 70.4, 128.3, 128.59, 128.62, 135.0, 154.1, 170.0, 171.4, 175.4

MS (EI) m/z: 296 (M^+)

MS (CI, i-C_4H_{10}) m/z: 297 (MH^+)

Elemental analysis; Calcd: C, 56.75%; H, 5.45%

Found: C, 55.91%; H, 5.59%

Specific rotation: $[\alpha]^{25}_D$ -1.77° (c 2.53, $CHCl_3$)

Reference example 1 (Synthesis of optically active monomethyl ~~3-(S)-~~(S)-3-hydroxyglutarate)

PAGE 20

Please replace the paragraphs beginning at line 28, through page 22, line 1, with the following new paragraphs:

To 700 mg (1.07 mmol) of dimethyl 3-benzoyloxycarbonyloxyglutarate were added 7 ml of an aqueous enzyme solution into which 0.7 mg of a lipase (CAL; available from Roche AG, Chirazyme L-2 (trade name)) originated from *Candida Antarctica* is dissolved and 189 mg (2.26 mmol) of sodium hydrogen carbonate, and the mixture was reacted under stirring at 30°C for 2 hours. After completion of the reaction, 7 ml of ethyl acetate was added to the resulting reaction mixture, a pH of the aqueous layer was adjusted to 1.7 by using 2 mol/L hydrochloric acid, 300 mg of sodium chloride was added thereto and the organic layer was extracted. The obtained organic layer was dried, filtered, and then, concentrated under reduced pressure to obtain an oily substance. The obtained oily substance was purified by silica gel column chromatography (Wakogel C-200 (trade name), n-hexane/ethyl acetate=1/9 (volume ratio)) to obtain 655 mg (isolation yield based on dimethyl 3-benzyloxycarbonyloxyglutarate=98%) of optically active monomethyl ~~3-(S)-~~(S)-3-benzyloxycarbonyloxyglutarate.

Then, 655 mg of the obtained optically active monomethyl 3-(S)-benzyloxycarbonyloxyglutarate was dissolved in 6 ml of methanol. To the mixture was added 24 mg of 10% palladium/carbon powder, and the mixture was reacted under normal pressure and hydrogen atmosphere at room temperature for 2 hours under stirring. After completion of the reaction, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain 351 mg (isolation yield based on optically active monomethyl ~~3-(S)-~~(S)-3-

benzyloxycarbonyloxyglutarate=98%) of optically active monomethyl ~~3-(S)-~~(S)-3-hydroxyglutarate.

Incidentally, physical properties of the optically active monomethyl ~~3-(S)-~~(S)-3-hydroxyglutarate were as follows.

^{1}H-NMR (δ (ppm), $CDCl_3$): 2.59 (d, 2H, J=5.86Hz), 2.60 (d, 2H, J=6.34Hz), 3.49 (s, 1H), 3.73 (s, 3H), 4.48 (quintet, 1H, 6.35), 5.49 (brs, 1H)

^{13}C-NMR (δ (ppm), $CDCl_3$): 40.3, 40.4, 52.0, 64.6, 172.3, 176.4

MS (CI, i-C_4H_{10}) m/z: 163 (MH^+)

Specific rotation: $[\alpha]^{22}_D$ +0.84° (c 4.19,$CHCl_3$)

Incidentally, absolute configuration was determined by comparing the specific rotation of the obtained optically active monomethyl ~~3-(S)-~~(S)-3-hydroxyglutarate and a sign of the specific rotation (literal value: $[\alpha]^{25}_D$ -0.43° (c 7.5, $CHCl_3$)) of optically active monomethyl ~~3-(R)-~~(R)-3-hydroxyglutarate described in Canadian Journal of Chemistry (Can. J. Chem.), 66, 1422 (1988).